Access DB# [redacted]

SEARCH REQUEST FORM

Scientific and Technical Information Center

85646

Requester's Full Name: Zohreh Fay (STIC) Examiner #: 66646 Date: 1/29/03
Art Unit: 1614 Phone Number 308-4604 Serial Number: 10/073,838 B
Mail Box and Bldg/Room Location: _____ Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need. 1 2

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: 8-ISO prostaglandins for glaucoma Therapy

Inventors (please provide full names): Steven Podos, Thomas Mittag, Bernard Becker

Earliest Priority Filing Date: 5/9/97

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

[redacted]

2) please search the claimed compound for the claimed use.

Thank you
Fay

Jan

Rush Board Approved
TC Page
SPE, AU 1615

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

****

STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher:		NA Sequence (#)		STN
Searcher Phone #:		AA Sequence (#)		Dialog
Searcher Location:		Structure (#)	✓	Questel/Orbit
Date Searcher Picked Up:	1/30/03	Bibliographic		Dr.Link
Date Completed:	1/30/03	Litigation		Lexis/Nexis
Searcher Prep & Review Time:		Fulltext		Sequence Systems
Clerical Prep Time:		Patent Family		WWW/Internet
Online Time:	100	Other		Other (specify)

PTO-1590 (8-01)

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FILE 'REGISTRY' ENTERED AT 17:58:41 ON 30 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2003 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   29 JAN 2003  HIGHEST RN 483275-57-6
DICTIONARY FILE UPDATES:  29 JAN 2003  HIGHEST RN 483275-57-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available.  See HELP
PROPERTIES for more information.  See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d sta que l33
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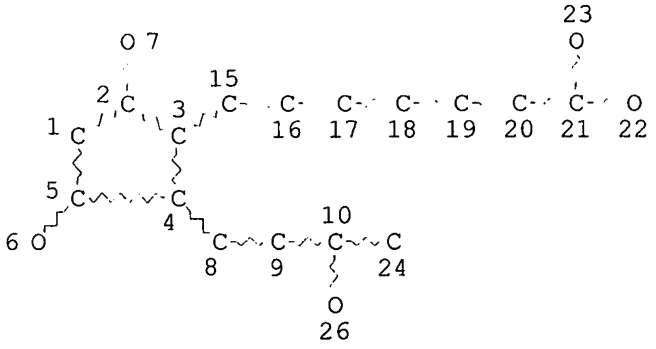


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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  21

STEREO ATTRIBUTES: NONE
L3          4523 SEA FILE=REGISTRY CSS FUL L1
L4                STR
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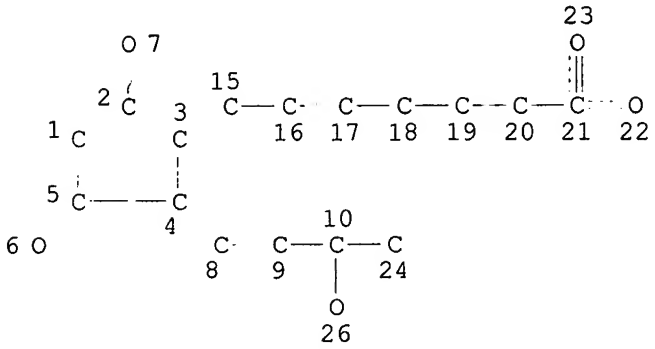
Jon Delaval
Science Librarian
Biochemistry & Chemical Library
Phone: 571-272-0428
jon.delaval@uspto.gov



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STEREO ATTRIBUTES: NONE
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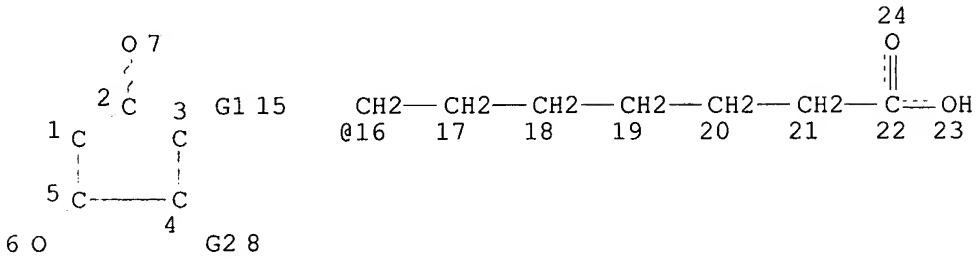

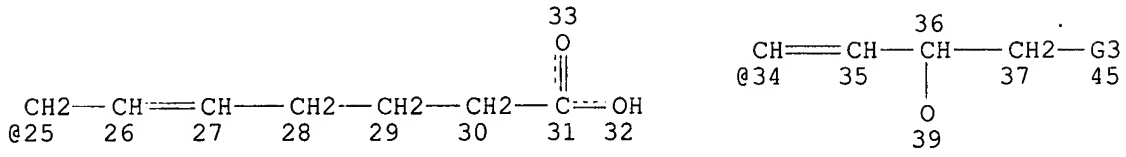

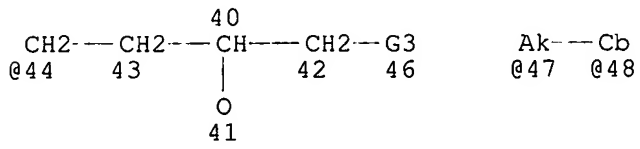

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VAR G2=44/34
VAR G3=AK/CB/47/48
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DEFAULT ECLEVEL IS LIMITED

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RING(S) ARE ISOLATED OR EMBEDDED

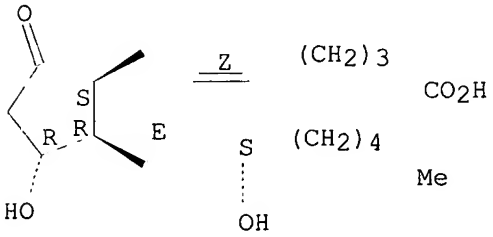
NUMBER OF NODES IS 41

STEREO ATTRIBUTES: NONE
L32 667 SEA FILE=REGISTRY SUB=L5 CSS FUL L31
L33 7 SEA FILE=REGISTRY ABB=ON PLU=ON L32 AND 8 ISO?

=> d ide can tot l33

L33 ANSWER 1 OF 7 REGISTRY COPYRIGHT 2003 ACS
RN 31660-17-0 REGISTRY
CN Prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo-, (5Z,8.beta.,11.alpha.,13E,15S)-(.+-.)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Heptenoic acid, 7-[3-hydroxy-2-(3-hydroxy-1-octenyl)-5-oxocyclopentyl]-, stereoisomer (8CI)
OTHER NAMES:
CN **(.+-.)-8-Iso-PGE2**
FS STEREOSEARCH
MF C20 H32 O5
LC STN Files: BEILSTEIN*, CA, CAPLUS, IFICDB, IFIPAT, IFIUDB, USPATFULL
(*File contains numerically searchable property data)

Relative stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

11 REFERENCES IN FILE CA (1962 TO DATE)
11 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 89:197010

REFERENCE 2: 86:120875

REFERENCE 3: 86:106037

REFERENCE 4: 86:72018

REFERENCE 5: 86:43275

REFERENCE 6: 86:43274

REFERENCE 7: 86:43273

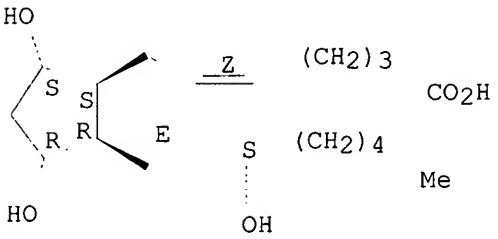
REFERENCE 8: 86:43272

REFERENCE 9: 86:43271

REFERENCE 10: 86:29419

L33 ANSWER 2 OF 7 REGISTRY COPYRIGHT 2003 ACS
RN 27415-26-5 REGISTRY
CN Prosta-5,13-dien-1-oic acid, 9,11,15-trihydroxy-,
(5Z,8.beta.,9.alpha.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Heptenoic acid, 7-[3,5-dihydroxy-2-(3-hydroxy-1-octenyl)cyclopentyl]-
(8CI)
OTHER NAMES:
CN 15-F2t-Isoprostane
CN 8-epi-PGF2.alpha.
CN 8-epi-Prostaglandin F2.alpha.
CN **8-Iso-PGF2.alpha.**
CN **8-iso-Prostaglandin F2.alpha.**
CN **8-Isoprostaglandin F2.alpha.**
CN Isoprostaglandin F2.alpha. type-III
FS STEREOSEARCH
MF C20 H34 O5
LC STN Files: ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT,
CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CSCHEM, EMBASE, MEDLINE,
TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



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355 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:37184

REFERENCE 2: 138:24095

REFERENCE 3: 138:19860

REFERENCE 4: 138:13506

REFERENCE 5: 137:367829

REFERENCE 6: 137:350753

REFERENCE 7: 137:346763

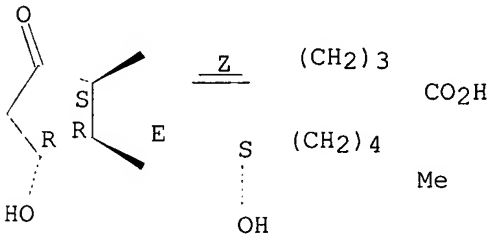
REFERENCE 8: 137:345874

REFERENCE 9: 137:310717

REFERENCE 10: 137:273303

L33 ANSWER 3 OF 7 REGISTRY COPYRIGHT 2003 ACS
RN 27415-25-4 REGISTRY
CN Prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo-, (5Z,8.beta.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Heptenoic acid, 7-[3-hydroxy-2-(3-hydroxy-1-octenyl)-5-oxocyclopentyl]-, stereoisomer (8CI)
OTHER NAMES:
CN **8-Iso-PGE2**
CN **8-Isoprostaglandin E2**
FS STEREOSEARCH
MF C20 H32 O5
LC STN Files: BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CHEMCATS, CSCHEM, EMBASE, MEDLINE, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.



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66 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:150553

REFERENCE 2: 137:77200

REFERENCE 3: 137:16027

REFERENCE 4: 136:32048

REFERENCE 5: 135:236932

REFERENCE 6: 135:147536

REFERENCE 7: 135:29381

REFERENCE 8: 134:361713

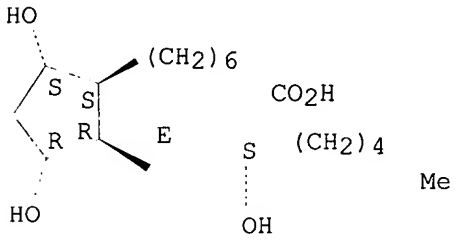
REFERENCE 9: 134:188516

REFERENCE 10: 134:126406

L33 ANSWER 4 OF 7 REGISTRY COPYRIGHT 2003 ACS
RN 26771-96-0 REGISTRY
CN Prost-13-en-1-oic acid, 9,11,15-trihydroxy-, (8.beta.,9.alpha.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:
CN Cyclopentaneheptanoic acid, 3,5-dihydroxy-2-(3-hydroxy-1-octenyl)-, stereoisomer (8CI)
OTHER NAMES:
CN 8-Epi-PGF1.alpha.
CN **8-Isoprostaglandin F1.alpha.**
FS STEREOSEARCH
MF C20 H36 O5
LC STN Files: BEILSTEIN*, CA, CAPLUS, CHEMCATS, CSCHEM, IFICDB, IFIPAT, IFIUDB, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



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18 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:247522

REFERENCE 2: 137:150553

REFERENCE 3: 135:29381

REFERENCE 4: 134:880

REFERENCE 5: 132:232274

REFERENCE 6: 127:76160

REFERENCE 7: 99:206351

REFERENCE 8: 98:628

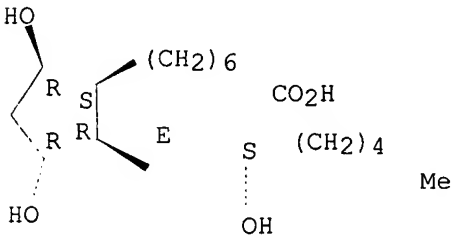
REFERENCE 9: 96:15330

REFERENCE 10: 90:201042

L33 ANSWER 5 OF 7 REGISTRY COPYRIGHT 2003 ACS
RN 26771-95-9 REGISTRY
CN Prost-13-en-1-oic acid, 9,11,15-trihydroxy-, (8.beta.,9.beta.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclopentaneheptanoic acid, 3,5-dihydroxy-2-(3-hydroxy-1-octenyl)-, stereoisomer (8CI)
OTHER NAMES:
CN **8-Isoprostaglandin F1.beta.**
FS STEREOSEARCH
MF C20 H36 O5

LC STN Files: BEILSTEIN*, CA, CAPLUS, CHEMCATS, IFICDB, IFIPAT, IFIUDB, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.



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10 REFERENCES IN FILE CA (1962 TO DATE)
10 REFERENCES IN FILE CAPLUS (1962 TO DATE)

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REFERENCE 2: 135:29381

REFERENCE 3: 134:880

REFERENCE 4: 127:76160

REFERENCE 5: 73:109365

REFERENCE 6: 73:3535

REFERENCE 7: 72:132154

REFERENCE 8: 72:109830

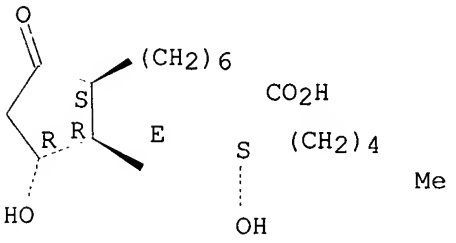
REFERENCE 9: 72:100143

REFERENCE 10: 72:100140

L33 ANSWER 6 OF 7 REGISTRY COPYRIGHT 2003 ACS
RN 21003-46-3 REGISTRY
CN Prost-13-en-1-oic acid, 11,15-dihydroxy-9-oxo-, (8.beta.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Cyclopentaneheptanoic acid, 3-hydroxy-2-(3-hydroxy-1-octenyl)-5-oxo-, stereoisomer (8CI)
OTHER NAMES:
CN **11.alpha.,15-(S)-Dihydroxy-9-oxo-13-trans-8-isoprostenoic acid**
CN **8-Iso-PGE1**
CN **8-iso-PGE1**
CN **8-Isoprostaglandin E1**
CN Isoprostaglandin E1
CN Ovinonic acid
FS STEREOSEARCH
DR 23756-23-2
MF C20 H34 O5
LC STN Files: BEILSTEIN*, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, CSCHEM, EMBASE, IFICDB, IFIPAT, IFIUDB, TOXCENTER, USPATFULL

(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.



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40 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 137:150553

REFERENCE 2: 135:29381

REFERENCE 3: 134:188516

REFERENCE 4: 134:880

REFERENCE 5: 132:232274

REFERENCE 6: 131:238301

REFERENCE 7: 130:13467

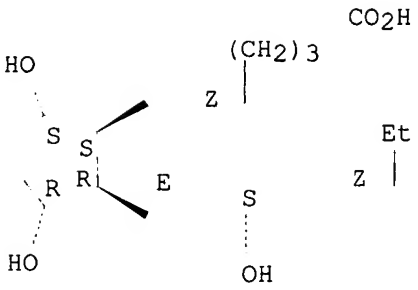
REFERENCE 8: 130:10658

REFERENCE 9: 129:131581

REFERENCE 10: 128:304157

L33 ANSWER 7 OF 7 REGISTRY COPYRIGHT 2003 ACS
RN 7045-31-0 REGISTRY
CN Prosta-5,13,17-trien-1-oic acid, 9,11,15-trihydroxy-, (5Z,8.beta.,9.alpha.,11.alpha.,13E,15S,17Z)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5-Heptenoic acid, 7-[3.alpha.,5.alpha.-dihydroxy-2-(3-hydroxy-1,5-octadienyl)cyclopentyl]- (7CI, 8CI)
OTHER NAMES:
CN **8-Iso-PGF3.alpha.**
FS STEREOSEARCH
MF C20 H32 O5
LC STN Files: BEILSTEIN*, CA, CAOLD, CAPLUS, CHEMCATS, TOXCENTER
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.



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13 REFERENCES IN FILE CAPLUS (1962 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 136:335491

REFERENCE 2: 135:29381

REFERENCE 3: 134:361713

REFERENCE 4: 134:126402

REFERENCE 5: 134:880

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REFERENCE 7: 131:252650

REFERENCE 8: 131:238301

REFERENCE 9: 130:320932

REFERENCE 10: 127:171810

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 17:59:02 ON 30 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 30 Jan 2003 VOL 138 ISS 5
FILE LAST UPDATED: 29 Jan 2003 (20030129/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all hitstr tot l61

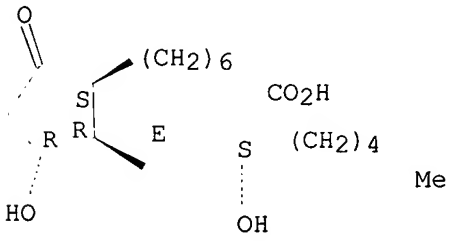
L61 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:744935 HCAPLUS
DN 130:10658
TI **8-Isoprostaglandins** for **glaucoma** therapy
IN **Podos, Steven M.; Mittag, Thomas W.; Becker, Bernard**
PA The Mount Sinai School of Medicine of the City University of New York, USA
SO PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-215
CC 1-12 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9850024	A1	19981112	WO 1998-US9090	19980506 <--
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9873686	A1	19981127	AU 1998-73686	19980506 <--
AU 725677	B2	20001019		
US 6037368	A	20000314	US 1998-73552	19980506 <--
EP 1007028	A1	20000614	EP 1998-920974	19980506 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI US 1997-853803	A2	19970509 <--		
WO 1998-US9090	W	19980506		

OS MARPAT 130:10658
AB The invention relates to the use of **8-isoprostaglandins** and their derivs. for decreasing intraocular pressure, e.g. in the treatment of **glaucoma**. It is based, at least in part, on the discovery that **8-isoprostaglandin** E2 effectively decreased intraocular pressure by a trabecular meshwork outflow mechanism.
ST isoprostaglandin **glaucoma** treatment
IT Drug delivery systems
Glaucoma (disease)
(isoprostaglandins for **glaucoma** therapy)
IT **Prostaglandins**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**isoprostaglandins** for **glaucoma** therapy)
IT **21003-46-3 21003-46-3D**, derivs. **27415-25-4 27415-25-4D**, derivs. **27415-26-5 27415-26-5D**, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(isoprostaglandins for **glaucoma** therapy)
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Bito; US 4599353 A 1986 HCAPLUS
IT **21003-46-3 21003-46-3D**, derivs. **27415-25-4 27415-25-4D**, derivs. **27415-26-5 27415-26-5D**, derivs.
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

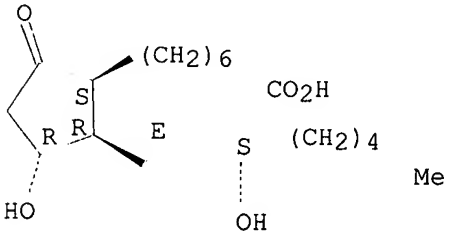
(Uses)
(isoprostaglandins for **glaucoma** therapy)
RN 21003-46-3 HCAPLUS
CN Prost-13-en-1-oic acid, 11,15-dihydroxy-9-oxo-,
(8.beta.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



RN 21003-46-3 HCAPLUS
CN Prost-13-en-1-oic acid, 11,15-dihydroxy-9-oxo-,
(8.beta.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



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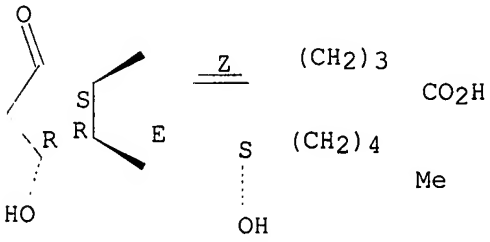
CN Prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo-,
(5Z,8.beta.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



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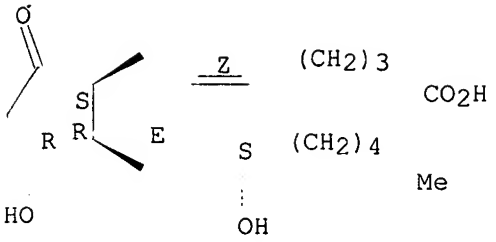
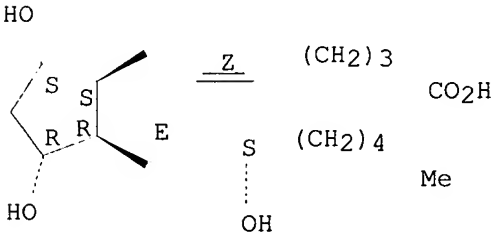
CN Prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo-,
(5Z,8.beta.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



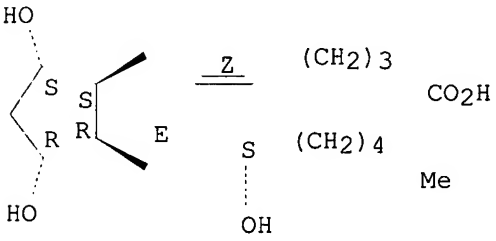
RN 27415-26-5 HCAPLUS
CN Prosta-5,13-dien-1-oic acid, 9,11,15-trihydroxy-, (5Z,8.beta.,9.alpha.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



RN 27415-26-5 HCAPLUS
CN Prosta-5,13-dien-1-oic acid, 9,11,15-trihydroxy-, (5Z,8.beta.,9.alpha.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



L61 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS
AN 1994:465605 HCAPLUS
DN 121:65605
TI Prostaglandins for the treatment of **glaucoma**
IN Woodward, David F.
PA Allergan, Inc., USA
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-557
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

PI	WO 9411002	A1	19940526	WO 1993-US10853	19931109	<--
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	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
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	AU 9455986	A1	19940608	AU 1994-55986	19931109	<--
PRAI	US 1992-975194	A	19921112 <--			
	WO 1993-US10853	W	19931109 <--			

OS MARPAT 121:65605

AB **Glaucoma** is treated by applying to the eye an amt. sufficient to treat **ocular hypertension** of prostaglandins of the D, E, and F series, or a pharmaceutically acceptable salt thereof. Intraocular pressure-reducing activities of 8-epi PGF2.alpha. and 8-epi PGF2.alpha. 1-Me ester were demonstrated with rabbits and monkeys.

ST ophthalmic prepn prostaglandin **glaucoma**

IT **Glaucoma (disease)**
(treatment of, with ophthalmic prepns. contg. prostaglandins)

IT Prostaglandins
RL: BIOL (Biological study)
(D, ophthalmic prepns. contg., for treatment of **ocular hypertension**)

IT Prostaglandins
RL: BIOL (Biological study)
(E, ophthalmic prepns. contg., for treatment of **ocular hypertension**)

IT Prostaglandins
RL: BIOL (Biological study)
(F, ophthalmic prepns. contg., for treatment of **ocular hypertension**)

IT Pharmaceutical dosage forms
(ophthalmic, prostaglandins in, for treatment of **ocular hypertension**)

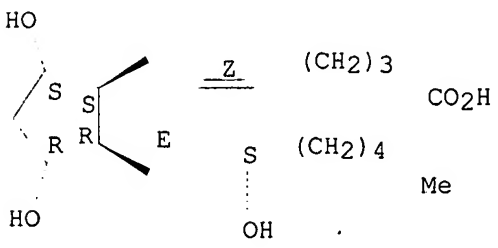
IT **27415-26-5** 96244-10-9
RL: BIOL (Biological study)
(ophthalmic prepns. contg., for treatment of **ocular hypertension**)

IT **27415-26-5**
RL: BIOL (Biological study)
(ophthalmic prepns. contg., for treatment of **ocular hypertension**)

RN 27415-26-5 HCAPLUS

CN Prosta-5,13-dien-1-oic acid, 9,11,15-trihydroxy-, (5Z,8.beta.,9.alpha.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



=> fil uspatall
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FILE 'USPAT2' ENTERED AT 18:13:09 ON 30 JAN 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

=> d bib ab kwic hitstr tot l86

L86 ANSWER 1 OF 2 USPATFULL
AN 2000:128385 USPATFULL
TI Method of treating **ocular hypertension** with 8-epi prostaglandins
IN Woodward, David F., El Toro, CA, United States
PA Allergan Sales, Inc., Irvine, CA, United States (U.S. corporation)
PI US 6124353 20000926
AI US 1992-975194 19921112 (7)
DT Utility
FS Granted
EXNAM Primary Examiner: Cintins, Marianne
LREP Baran, Robert J., Voet, Martin A., Fisher, Carlos A.
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 554
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a method of treating **ocular hypertension** which comprises applying to the eye an amount sufficient to treat **ocular hypertension** of a compound of formula (I) ##STR1## wherein the wavy line attachments indicate either alpha (.alpha.) or beta (.beta.) configuration; hatched lines indicate .alpha. configuration, solid triangles are used to indicate .beta. configuration; the dashed bonds represent a single bond or a double bond which can be in the cis or trans configuration; X is selected from the group consisting of H, R or a pharmaceutically-acceptable cation, and R is an aliphatic hydrocarbon group of about 1 to about 6 carbon atoms; one of R.sub.1 and R.sub.2 is .dbd.O, --OH or an --O(CO)R.sub.4 group, and the other one is --OH or an --O(CO)R.sub.4 group or R.sub.1 is .dbd.O and R.sub.2 is H; R.sub.3 is --OH or --O(CO)R.sub.4, wherein R.sub.4 is a saturated or unsaturated acyclic hydrocarbon group having from 1 to about 20 carbon atoms, or --(CH.sub.2).sub.n R.sub.5 wherein n is 0-10, and R.sub.5 is an aliphatic ring from about 3 to about 7 carbon atoms, or an aromatic or heteroaromatic ring; or a pharmaceutically acceptable salt thereof.
TI Method of treating **ocular hypertension** with 8-epi prostaglandins
AB The present invention provides a method of treating **ocular hypertension** which comprises applying to the eye an amount sufficient to treat **ocular hypertension** of a compound of formula (I) ##STR1## wherein the wavy line attachments indicate either alpha (.alpha.) or beta (.beta.) configuration;. . .
SUMM . . . prostaglandins and C-1 ester derivatives thereof. Such compounds are potent ocular hypotensives, and are particularly suitable for the management of **glaucoma**.
SUMM . . . useful in the treatment of a number of ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, **glaucoma**, and as presurgical adjuncts.
SUMM **Glaucoma** is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, **glaucoma** has been classified as primary or secondary. For example, primary **glaucoma** in adults (congenital **glaucoma**) may be either open-angle or acute or chronic angle-closure. Secondary **glaucoma** results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.
SUMM The underlying causes of primary **glaucoma** are not yet known. The increased intraocular tension is due to the obstruction of aqueous

humor outflow. In chronic open-angle **glaucoma**, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure **glaucoma**, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the. . . produce pupillary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure **glaucoma** attacks of various degrees of severity.

SUMM Secondary **glaucoma** is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and. . .

SUMM Considering all types together, **glaucoma** occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing. . . vision. In cases where surgery is not indicated, topical .beta.-adrenoreceptor antagonists have traditionally been the drugs of choice for treating **glaucoma**.

SUMM . . . shows that some prostaglandins are highly effective ocular hypotensive agents, and are ideally suited for the long-term medical management of **glaucoma** (see, for example, Bito, L. Z. Biological Protection with Prostaglandins Cohen, M. M., ed., Boca Raton, Fla., CRC Press Inc., 1985, pp. 231-252; and Bito, L. Z., Applied Pharmacology in the Medical Treatment of **Glaucomas** Drance, S. M. and Neufeld, A. H. eds., New York, Grune & Stratton, 1984, pp. 477-505). Such prostaglandins include PGF.sub.2.alpha.,. . .

SUMM . . . C.sub.5 alkyl esters of the latter compound, were reported to possess ocular hypotensive activity and were recommended for use in **glaucoma** management. It was suggested that the C.sub.1 to C.sub.5 alkyl esters of PGF.sub.2.alpha., such as its methyl and isopropyl esters,. . .

SUMM . . . 1-isopropyl ester, in humans. The clinical potentials of prostaglandins in the management of conditions associated with increased ocular pressure, e.g. **glaucoma** are greatly limited by these side effects.

SUMM In one aspect, the present invention relates to a method of treating **ocular hypertension** which comprises applying to the eye an amount sufficient to treat **ocular hypertension** of a compound of formula (I) ##STR2## wherein the wavy line attachments indicate either alpha (.alpha.) or beta (.beta.) configuration;. . .

SUMM In a preferred embodiment, such pharmaceutical compositions are in the form of ophthalmic solutions for the treatment of **ocular hypertension**, comprising an amount sufficient to treat **ocular hypertension** of a compound of formula (I) as hereinabove defined, or a pharmaceutically acceptable salt thereof.

CLM What is claimed is:

1. A method of treating **ocular hypertension** which comprises applying to the eye an amount sufficient to treat **ocular hypertension** of a compound of formula (I) while lowering hyperemia as compared to the corresponding iso form of the compound ##STR7##. . .

11. The pharmaceutical composition of claim 10 wherein said aqueous solution is an ophthalmic solution.for the treatment of **ocular hypertension** comprising an amount sufficient to treat **ocular hypertension** of said compound of formula (I) or an ophthalmically acceptable salt thereof.

IT **Glaucoma (disease)**
(treatment of, with ophthalmic prepns. contg. prostaglandins)

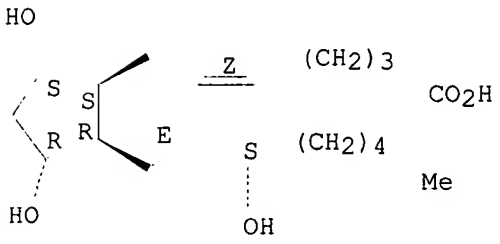
IT **27415-26-5** 96244-10-9
(ophthalmic prepns. contg., for treatment of ocular hypertension)

IT **27415-26-5**
(ophthalmic prepns. contg., for treatment of ocular hypertension)

RN 27415-26-5 USPATFULL

CN Prosta-5,13-dien-1-oic acid, 9,11,15-trihydroxy-, (5Z,8.beta.,9.alpha.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



L86 ANSWER 2 OF 2 USPATFULL
AN 2000:31442 USPATFULL
TI 8-iso- prostaglandins for **glaucoma** therapy
IN Podos, Steven M., Tenafly, NJ, United States
Mittag, Thomas W., Pleasantville, NY, United States
Becker, Bernard, University City, MO, United States
PA Mount Sinai School of Medicine, New York, NY, United States (U.S. corporation)
PI US 6037368 20000314
AI US 1998-73552 19980506 (9)
RLI Continuation of Ser. No. US 1997-853803, filed on 9 May 1997, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Fay, Zohreh
LREP Bakerbotts LLP
CLMN Number of Claims: 21
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 381
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the use of 8-iso prostaglandins and their derivatives for decreasing intraocular pressure, for example in the treatment of **glaucoma** It is based, at least in part, on the discovery that 8-iso prostaglandin E.sub.2 effectively decreased intraocular pressure by a trabecular meshwork outflow mechanism.
TI 8-iso- prostaglandins for **glaucoma** therapy
AB . . . relates to the use of 8-iso prostaglandins and their derivatives for decreasing intraocular pressure, for example in the treatment of **glaucoma** It is based, at least in part, on the discovery that 8-iso prostaglandin E.sub.2 effectively decreased intraocular pressure by a. . .
SUMM . . . relates to the use of 8-iso prostaglandins and their derivatives for decreasing intraocular pressure, for example in the treatment of **glaucoma**. It is based, at least in part, on the discovery that 8-iso prostaglandin E.sub.2 effectively decreased intraocular pressure by a. . .
SUMM **Glaucoma** is a major eye disease which can cause progressive loss of vision leading to blindness. The majority of human **glaucomas** are associated with increased intraocular pressure ("IOP") resulting from an imbalance in the rate of secretion of aqueous humor by. . . humor outflow from these chambers, primarily via the canal of Schlemm. High IOP is considered the major risk factor for **glaucomatous** visual impairment resulting from the death of retinal ganglion cells, loss of the nerve fiber layer in the retina, and. . .
SUMM **Glaucoma** is typically classified, on the basis of its

etiology, as primary or secondary. Primary **glaucoma** in adults, a disorder in which the underlying cause is poorly understood, is associated with increased IOP due to an. . . open angle or acute or chronic angle closure. The anterior chamber of the eye appears normal in chronic open angle **glaucoma**, despite impaired drainage of aqueous humor. In contrast, the anterior chamber is shallow and the filtration angle is narrowed in chronic angle-closure **glaucoma**, wherein the trabecular meshwork and the canal of Schlemm may be obstructed by the iris. An acute attack of **glaucoma** may arise in this context when the pupil dilates, pushing the root of the iris forward to block the angle.

SUMM Secondary **glaucoma** is caused by another disorder which functionally interferes with the outflow of aqueous humor or the flow from the posterior. . .

SUMM . . . decreasing the formation of aqueous humor within the eye. Pilocarpine and epinephrine are clinical agents that also lower IOP in **glaucomatous** eyes, but these drugs act principally by decreasing the resistance in the trabecular meshwork outflow channels. A third mechanism for. . . prostaglandin derivative belonging to the F2.alpha. series of prostanoids, which acts primarily by this uveoscleral mechanism, has been introduced for **glaucoma** therapy. This drug, called latanoprost, is the isopropyl ester of a compound having the following structure: ##STR1##

SUMM Prostaglandins which may be used in the treatment of **glaucoma** are described in U.S. Pat. Nos. 5,476,872 by Garst et al., 4,599,353 by Bito, 5,262,437 by Chan, 5,462,968 by Woodward,. . .

SUMM The present invention relates to prostaglandins which are structurally different from latanoprost and other prostaglandins used in the treatment of **glaucoma**, and that belong to the 8-iso series of prostanoids, for example 8-iso PGE.sub.2, 8-iso PGE.sub.2 and 8-iso-PGF.sub.2.alpha.. In contrast to. . .

SUMM . . . use of 8-iso prostanoids in methods which decrease intraocular pressure ("IOP") in the eye, for example in the treatment of **glaucoma**. The 8-iso-prostanoids of the invention have a common structure according to formula I: ##STR2## where either bond W or bond. . .

SUMM . . . advantage in that the trabecular meshwork is the primary locus of the pathology causing increased IOP in primary open angle **glaucoma**.

SUMM . . . the invention to a subject in need of such treatment. Such a method may be used in the treatment of **glaucoma** in a subject. Suitable formulations include for example, and not by way of limitation, a topical solution which is a. . .

SUMM According to the invention, IOP may be decreased, and/or **glaucoma** may be treated, using compositions comprising an 8-iso prostanoid of the invention as the sole active agent, or in conjunction. . .

DETD Experiments were performed to evaluate the effects of single dose administration of 8-iso PGE.sub.2 on IOP in normal ("N") and **glaucomatous** ("G") monkey eyes, and to determine the mechanism by which 8-iso PGE.sub.2 alters IOP in N monkey eyes, when applied. . .

DETD Table 2 shows the effect of 8-iso PGE.sub.2 on IOP and outflow facility in **glaucomatous** monkey eyes. Because of the individual variability in laser-induced **glaucomatous** monkey eyes, the IOP and facility measurements are expressed in the table as ratios (value of the drug-treated eye.div.the value of the vehicle-treated eye). The ratios were calculated from the values of the same **glaucomatous** monkey eye determined immediately prior to administration of the drug or the vehicle (time 0 hrs.), and the values at. . . of the drug or vehicle. The data in Table 2 show that in the primate, administration of 8-iso PGE.sub.2 to **glaucomatous** eyes significantly lowers IOP (by 13.8%) and significantly increases outflow facility (by 38.8%),

which is of sufficient magnitude to account for the fall in IOP. Thus the mechanism of lowering IOP by 8-iso PGE.sub.2 in both normal and **glaucomatous** eyes is primarily due to an increase in aqueous humor trabecular outflow.

DETD TABLE 2

Effect of 0.1% 8-iso PGE.sub.2 on IOP and Outflow Facility Responses in 8 **Glaucomatous** Monkey Eyes (Unilateral)

	Intraocular Pressure		Outflow facility (drug-treated/ vehicle-treated)	
			(drug-treated/ vehicle treated)	
Time	0 hr	2 hr	0 hr	2 hr

Response. . .

DETD . . . single dose of 8-iso PGE, (the 13, 14 dihydro derivative of 8-iso PGE.sub.2), 8-iso PGE.sub.2, or 8-iso PGF.sub.2.alpha. in laser-induced **glaucomatous** eyes in cynomolgus monkeys (wherein only one eye is rendered **glaucomatous** and the other serves as a control). Following one day of baseline IOP measurement, a single 25 .mu.l dose of. . . percent 8-iso PGE.sub.1, or (ii) 0.1 percent 8-iso PGE.sub.2, or (iii) 0.1 percent 8-iso PGF.sub.2.alpha., was topically applied to the **glaucomatous** eye in groups of 4 or 8 monkeys. It was found that 8-iso PGE.sub.1 (0.1 percent) reduced IOP ($p<0.05$) for up to four hours in **glaucomatous** monkey eyes (n=4). The maximum reduction in IOP was 5.3.+-.0.8 (mean.+-.SEM) mm Hg at 2 hours after dosing. 8-iso PGE.sub.2. . . the compounds tested, 8-iso PGE.sub.2 appears to have the greatest and 8-iso PGF.sub.2.alpha.. the least activity in decreasing IOP in **glaucomatous** monkey eyes.

IT Drug delivery systems

IT **Glaucoma (disease)**
(isoprostaglandins for glaucoma therapy)

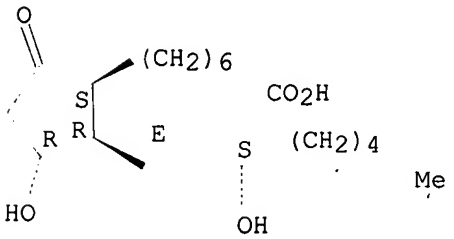
IT **21003-46-3 21003-46-3D**, derivs. **27415-25-4 27415-25-4D**, derivs. **27415-26-5 27415-26-5D**, derivs.
(isoprostaglandins for glaucoma therapy)

IT **21003-46-3 21003-46-3D**, derivs. **27415-25-4 27415-25-4D**, derivs. **27415-26-5 27415-26-5D**, derivs.
(isoprostaglandins for glaucoma therapy)

RN 21003-46-3 USPATFULL

CN Prost-13-en-1-oic acid, 11,15-dihydroxy-9-oxo-, (8.beta.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

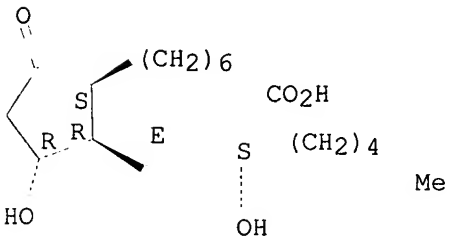
Absolute stereochemistry.
Double bond geometry as shown.



RN 21003-46-3 USPATFULL

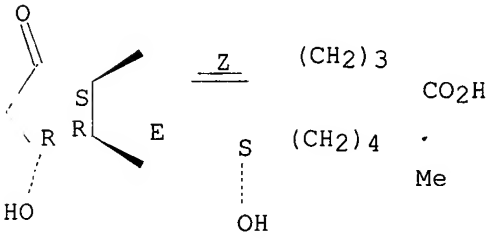
CN Prost-13-en-1-oic acid, 11,15-dihydroxy-9-oxo-, (8.beta.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



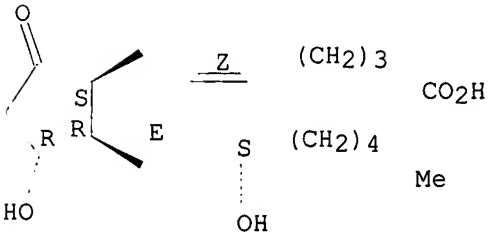
RN 27415-25-4 USPATFULL
CN Prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo-, (5Z,8.beta.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



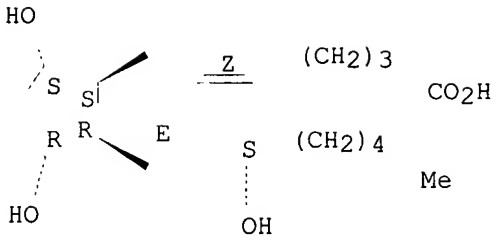
RN 27415-25-4 USPATFULL
CN Prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo-, (5Z,8.beta.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



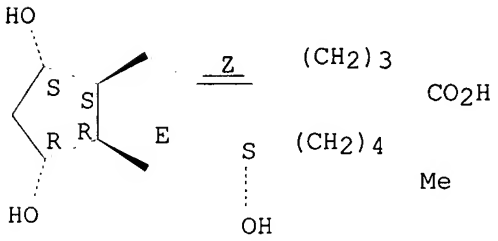
RN 27415-26-5 USPATFULL
CN Prosta-5,13-dien-1-oic acid, 9,11,15-trihydroxy-, (5Z,8.beta.,9.alpha.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



RN 27415-26-5 USPATFULL
CN Prosta-5,13-dien-1-oic acid, 9,11,15-trihydroxy-,
(5Z,8.beta.,9.alpha.,11.alpha.,13E,15S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



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SAV TEMP L5 FAY073A/A
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L8 STR L6
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E MITTAG T/AU

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L19       14388 S L15
L20           8 S L16-L18 AND L19
                SEL RN

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L26           2 S L23 NOT L22
L27           4 S L5 AND L21
L28           2 S L10 AND L21
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                E E4+ALL
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L43        4580 S E6-E9/BI
                E E10+ALL
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L45        1159 S E3-E6/BI
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                E PROSTAGLANDINS/CT
                E E3+ALL
L66       69795 S E51+NT
L67       59887 S L66,L62 AND PY<=1997
L68         196 S L67 AND L43,L45
                E GLAUCOMA/CT
                E E3+ALL
L69       23660 S E4+NT
                E E3+ALL
L70       24576 S E3+NT
L71         196 S L67 AND L43,L45
L72         162 S L67 AND L69,L70
L73         196 S L71,L72
L74           0 S L73 AND 8 ISO?
L75           3 S L65 AND L66
                E PROSTAGLANDINS F/CT
                E E4+ALL
L76        1270 S E52
L77          65 S L76 AND L73
                E PROSTAGLANDINS E/CT
                E E3=ALL
                E PROSTAGLANDINS E/CT
                E E3+ALL
L78       14072 S E50
                E PROSTAGLANDINS E/CT
                E E4+ALL
L79        1477 S E52
L80          18 S L73 AND L78,L79
L81           0 S L80 AND 8

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L82          21 S L33
L83           2 S L82 AND ?GLAUCOM?
L84           2 S L82 AND L43,L45
                E GLAUCOMA/CT
L85           2 S L82 AND E4
L86           2 S L83-L85

     FILE 'USPATFULL, USPAT2' ENTERED AT 18:13:09 ON 30 JAN 2003
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